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Please find below and/or attached an Office communication concerning this application or proceeding.

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/410,462
Filing Date: October 01, 1999
Appellant(s): WILLIAMS ET AL.

Gary R. Fabian
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/31/09 appealing from the Office action mailed 4/7/09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 6-11, 15, 17-20, 28, and 34 are pending. Claim 28 is allowed. Claims 8-10, 19, 20, and 34 are objected to. Claims 6, 7, 11, 15, 17, and 18 are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN

REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

U.S. Patent 6,080,578	Bischoff et al.	6-2000

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6, 7, 11, 15, 17, 18 are rejected under 35 U.S.C. 102(e) as being anticipated by anticipated by U.S. Patent No. 6,080,578 (Bischoff et al.).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37

CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Bischoff et al. anticipate the rejected claims because Bischoff et al. teach a method that comprises the active steps required by the claims which would necessarily result in the same outcome as the claimed method. That is, Bischoff et al. teach administering an adenovirus that meets the structural limitations of the claims to a tumor in an animal via various routes of administration including intravenous delivery. Specifically, Bischoff et al. teach a cytopathic adenovirus comprising a mutation in an E1A CR2 RB family member binding region as well as methods of using the vector for preferential therapy and prophylaxis of neoplastic (dividing) compared to non-neoplastic cells (e.g., column 3, lines 7-29; column 4, lines 1-55; etc.) Bischoff et al. teach that the mutant adenoviral vector can comprise a mutation that can be a deletion, substitution or frameshift mutation in the CR2 domain (specifically, amino acids 120-139 in Ad5) (see column 10, lines 10-25). Bischoff specifically teaches a mutant comprising a deletion of amino acids 2-150 (dl 1010) which completely deletes the CR1 and CR2 domains (see column 10, lines 25-40). Bischoff et al. teach that the mutant adenoviral vectors can be used to treat different types of tumors in a subject by administering the vector to the tumor, for instance by swabbing a solution comprising the vector directly on a tumor or by direct injection or intravenous administration (e.g., see column 16, lines 26-53). Administering the adenovirus to a tumor by means taught by Bischoff would necessarily result in administration of the vector to the blood vessels associated with the tumor, particularly when the administration is by intravenous delivery. Therefore, administering the adenovirus to a tumor as taught by Bischoff would

necessarily result in substantially and selectively killing dividing endothelial cells (including dividing microvasculature) as is claimed.

It is noted that MPEP § 2112 indicates,

> "[T]he claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."; and, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)."

Since the adenovirus used in the process taught by Bischoff et al. meets all of the structural limitations of the adenovirus used in the method of the instant claims, absent evidence to the contrary, it necessarily would have all of the same effects as the claimed adenovirus. Thus, the adenovirus of Bischoff would replicate to higher titers in dividing endothelial cells than a wild-type (non-mutant) adenovirus. It is noted that MPEP § 2112.01 indicates, "'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.' *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare

prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Furthermore, since the claimed adenovirus and the adenovirus taught by Bischoff are structurally the same, administering the adenovirus directly on a tumor or by direct injection or intravenous administration, as taught by Bischoff would necessarily result in selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells.

In conclusion, Bischoff et al. anticipates all of the active steps of the claimed methods; therefore, the results of the claimed methods and the methods of Bischoff are necessarily the same, regardless if all results were recognized in the prior art.

(10) Response to Argument

Appellant argues that the instant claims are not anticipated by Bischoff et al. because Bischoff et al. does not expressly teach all of the elements of the present invention. Appellant contends that Bischoff et al. does not teach (i) a limitation relating to preferential killing of dividing endothelial cells compared to quiescent endothelial cells, and (ii) a limitation that the claimed method is carried out by direct administration of a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region to endothelial cells. Appellant further asserts that Bischoff et al. does not teach that the mutant adenovirus versus wild-type virus replicates to higher titers in the dividing endothelial cells or that the method would "control angiogenesis in an animal". Appellant argues that although Bischoff teaches a composition comprising a recombinant adenovirus which is substantially replication deficient in non-neoplastic cells and which exhibits at least partial replication phenotype in neoplastic cells,

as well as methods of using the adenovirus composition, Bischoff does not teach that the replication competent adenovirus demonstrates enhanced replication in and killing of dividing endothelial cells versus quiescent endothelial cells or direct administration of a mutant adenovirus to endothelial cells. Appellant contends that a *prima facie* case of inherency has not been established and asserts that Bischoff must be modified in order to teach the claimed invention. Specifically, Appellant argues that Bischoff only teaches the use of E1A-$RB^{(-)}$ adenovirus mutants in methods of ablating $RB^{(-)}$ neoplastic cells and assert that it is not inherent to infect endothelial cells or other types (non-$RB^{(-)}$) tumor cells with the mutant adenovirus. Appellant asserts that the claimed invention is not a natural result flowing from the reference of Bischoff et al. because the reference contains no explicitly explicated limitations from which the natural result would be preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, including microvascular endothelial cells.

In response, it is respectfully pointed out that Appellant does not take issue with the notion that the adenovirus of Bischoff et al. meets the structural limitations of the claimed adenovirus.

Furthermore, it is respectfully noted that a chemical composition and its properties are inseparable; therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present (See MPEP § 2112.01, *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)), as are their processes and yields (*In re Von Schickh*, 362 F.2d 821, 150 USPQ 300 (CCPA 1966). Moreover, the court in *Integra Life Sciences I Ltd. v. Merck KGaA,* 50 USPQ2d 1846 (DC SCalif, 1999) held that a reference teaching a process may anticipate claims drawn to a method comprising the same process steps,

despite the recitation of a different intended use in the preamble or the later discovery of a particular property of one of the starting materials or end products.

In order to clarify the location of endothelial cells, it is respectfully pointed that, in the Appeal Brief, Appellant states:

> "The endothelium comprises a single layer of flat cell that line the interior surface of blood vessels. The endothelium forms an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells are the cells that make up the inside of blood vessels. Angiogenesis is the formation of new blood vessels. Angiogenesis has come to be appreciated as a continuous and important process in tumor development." (See page 16).

It is also respectfully noted that the specification of the instant application discloses:

> "Critical to tumor growth and metastasis is angiogenesis. Angiogenesis is necessary for growth and metastasis of the primary tumor as well as subsequent metastasis of secondary tumors. That is, a tumor cannot maintain sustained growth without a blood supply to provide nutrients, and remove metabolic wastes. Thus, formation of new blood vessels, or angiogenesis, facilitates tumor cell growth, allows tumor cells to gain entry to the blood stream, and to circulate throughout the body. Thus, inhibition or prevention of angiogenesis is expected to be an effective method for preventing tumor growth and metastasis.
> It is worth noting that as part of the angiogenesis process, tumor-associated endothelial cells proliferate while endothelial cells associated with normal tissues are essentially quiescent..." (See page 2, lines 21-30).

Therefore, it is clear that in endothelial cells line the interior surface of blood vessels and angiogenesis (i.e., the formation of blood vessels) is associated with growing tumors. As such, blood vessels containing endothelial cells would be present in a growing tumor. Furthermore, the endothelial cells of the growing blood vessels associated with the tumor would be dividing.

Bischoff et al. teach a method of delivering a mutant adenovirus (i.e., an adenovirus that is encompassed by the claims) to a tumor wherein the mutant adenovirus is administered to the tumor intravenously. Bischoff specifically indicates that the mutant adenovirus can be administered into the portal vein for delivery of the adenovirus to hepatocarcinoma or liver

metastases (both of which are tumors located in the liver). Since blood vessels are lined with endothelial cells, administering the mutant adenovirus intravenously for deliver to the tumor (e.g., into the portal vein for liver tumors) would necessarily include directly administering the adenovirus to endothelial cells, including dividing endothelial in the growing vessels in the tumor (including tumor microvasculature endothelium). Therefore, Bischoff et al. teach a method comprising administering a mutant adenovirus (i.e., one that is the same as the claimed adenovirus) to a tumor by intravenous administration of the adenovirus which would necessarily result in the adenovirus directly contacting dividing endothelial cells including microvascular endothelial cells. Although Bischoff et al. does not explicitly teach that the method results in killing dividing endothelial cells with less killing of non-dividing endothelial cells (and substantial and selective killing of microvascular endothelial cells compared to quiescent microvascular endothelial cells) this is considered an inherent property of Bischoff's mutant adenovirus that was not recognized by Bischoff at that time. Therefore, Bischoff et al. teaches a method comprising all of the steps necessary to deliver the mutant adenovirus to a population of cells comprising dividing and non-dividing endothelial cells and performing these method steps would necessarily result in selective killing of dividing endothelial cells (and dividing microvascular endothelial cells) compared to non-dividing endothelial cells (and non-dividing microvascular endothelial cells) which would necessarily result in controlling angiogenesis; furthermore, the mutant adenovirus would necessarily replicate to higher titers in dividing endothelial cells versus wild-type virus.

In response to applicant's argument that it is not inherent to infect endothelial cells or other types (non-$RB^{(-)}$) tumor cells with the mutant adenovirus, it is noted that (1) intravenous

administration of the adenovirus would necessarily result in the adenovirus directly contacting endothelial cells as endothelial cells line the interior of blood vessels, and (2) the rejected claims do not required that the adenovirus is administered to any specific type of tumor (i.e., there is no requirement in the claims the adenovirus is administered to non-$RB^{(-)}$ tumor cells). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Therefore, the teachings of Bischoff et al. are sufficient to anticipate the rejected claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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